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PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Arguello *et al.*

Appl. No.: 09/077,615

Filing Date: October 23, 1998

Title: METHODS FOR SEPARATING AND/OR IDENTIFYING DNA MOLECULES

Docket No.: 028979-0103

Commissioner for Patents  
Washington, D.C. 20231

"Express Mail" Mailing Label No.: 74208236711US  
Date of Deposit: April 23, 2003

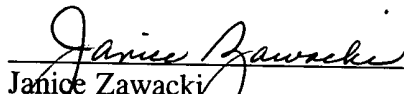
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Atty. Docket No. 028979-0103

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants: Rafael ARGUELLO *et al.*

Title: METHODS FOR SEPARATING AND/OR IDENTIFYING DNA MOLECULES

Appl. No.: 09/077,615

Filing Date: 10/23/1998

Examiner: J. C. Einsmann

Art Unit: 1634

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BRIEF IN REPLY TO EXAMINER'S ANSWER

Commissioner for Patents  
Washington, D.C. 20231

Dear Sir:

This brief is respectfully submitted in accordance with 37 C.F.R. § 1.193(b) in reply to the Examiner's Answer mailed February 26, 2003. The required fee for filing this reply brief, as set forth in 37 C.F.R. § 1.17(c), is included in Check No. 761227. No additional fee is believed to be due for this filing. Any fee deficiency may be charged, or overpayment credited to, Deposit Account No. 50-2350. This brief is transmitted in triplicate. Appellants acknowledge the Examiner's withdrawal of the rejection of the claims under 35 U.S.C. §112, second paragraph.

1. **The claims are not obvious over Zimmerman *et al.* in view of Sapirstein *et al.***

In the Examiner's Answer, the rejection of claims 55-59 and 73-76 was maintained "under 35 U.S.C. 103(a) as being unpatentable over Zimmerman *et al.* in view of Sapirstein *et al.* (Seed Science Technology (1986) 14(3) 489-517)." This rejection is improper because it does not meet the standard for a legal case of obviousness under 35 U.S.C. §103.

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First and foremost, this rejection is based on an impermissible hindsight reconstruction of the claimed invention. This is readily apparent because the Examiner has not considered the claimed invention as a whole, or the entire teachings of the cited references.

When applying 35 U.S.C. §103 “the following tenets of patent law that must be adhered to...:

- (1) the claimed invention must be considered as a whole;
- (2) the references must be considered as a whole and suggest the desirability and thus the obviousness of making the combination; [and]
- (3) the references must be viewed without the benefit of hindsight vision afforded by the claimed invention[.]”

*Hodosh v. Block Drug Co.*, 786 F. 2d 1136, 1143 n. 5, 229 U.S.P.Q. 182, 187 n. 5 (Fed. Cir. 1986).

In her Answer, The Examiner states that “[i]n this case, Sapirstein *et al.* are pertinent to the particular problem with which appellant is concerned, namely, the use of a database of electrophoretic gel mobilities to make an identification of an unknown entity.” This statement clearly reflects that the Examiner has not considered the invention as a whole but instead viewed the claimed invention in distinct, separable pieces. Specifically, this statement completely disregards numerous steps of the claimed invention, namely elements (a)-(c) of claims 55-69 and elements (a)-(e) of claims 73-76. By ignoring these inseparable elements and only focusing on the desired portions of the presently claimed subject matter, the Examiner has improperly overstated the case that Sapirstein *et al.* is analogous to the claimed invention and the other cited art. However, the claimed invention may not be dissected into discrete elements to be analyzed in isolation, but must be considered as a whole. *See, e.g., W. L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F. 2d 1540,1548, 220 U.S.P.Q. 303, 309 (Fed. Cir. 1983); *Jones v. Hardy*, 727 F.2d 1524,1530, 220 U.S.P.Q. 1021,1026 (Fed. Cir. 1984). The skilled artisan considering the whole of the claimed invention would not consider Sapirstein *et al.* to be analogous art. The presently claimed invention identifies DNA

molecules at the molecular level. Sapirstein *et al.* do not identify anything at the molecular level but only used gliadin protein banding patterns, not specific individual proteins, for wheat cultivar identification. The present claims recite DNA hybridization. Sapirstein *et al.* include no hybridization step. The only apparent commonality between the present claims and Sapirstein *et al.* is the use of a database.

The Examiner also fails to consider the references as a whole when arguing for their combination. For example, the Examiner states that “in both references, the subject is to use the electrophoretic mobility of a particular molecule or molecules to make an identification.” This statement overly generalizes the teachings of the cited references to make them appear related. To one skilled in the art, human lymphocyte typing and wheat cultivar identification as disclosed in the cited references are not related. The Examiner admits as much stating “Appellant is entirely accurate in stating that there is a contrast between Zimmerman *et al.* and Sapirstein *et al.* in that one is looking at individual molecules and the other is using electrophoretic data to identify cultivars of wheat.” The only apparent similarity is that both references use electrophoresis. These references are not even electrophoresing the same molecules. Zimmerman *et al.* examined labeled, hybridized DNA molecules. Sapirstein *et al.* analyzed gliadin protein banding patterns. In focusing only on certain aspects of the references, the Examiner has also failed to address other differences between the cited references. For example, Sapirstein *et al.* rely on features not relevant to the teachings of Zimmerman *et al.*, such as complex statistical analysis and the subjective determination of “the intensity of the gliadin band(s)” as a “secondary feature” in the identification of wheat cultivars.

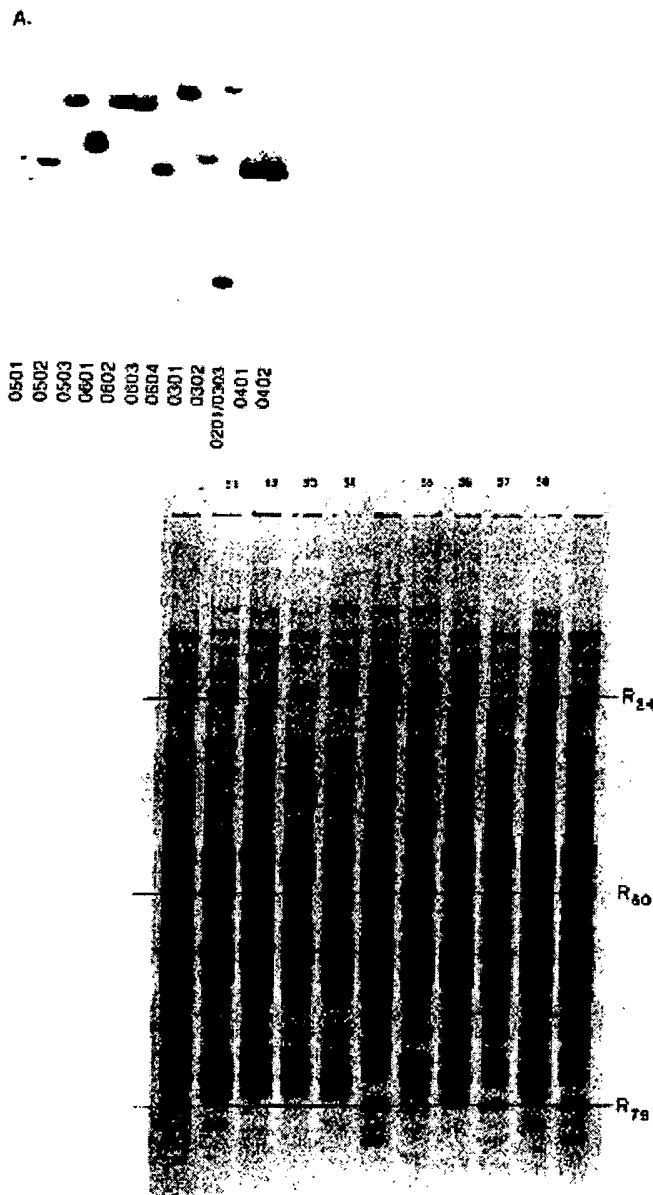
The Examiner makes other statements that reflect that she is not considering the claimed invention or the cited references in their entireties, for example, when she states that the:

examiner and appellant agree that Zimmerman *et al.* fail to teach steps (d) and (e) of the claim. Conceptually, what [Zimmerman *et al.*] do not teach is a method where an exact numerical value is assigned to the distance that the test duplex travels and then comparing that value to the values of previously tested known molecules for identification.

This statement reflects that Examiner is improperly the invention down to the conceptual “gist” or “core” of the invention, which is improper. *Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve, Inc.*, 796 F.2d 443, 449, 230 U.S.P.Q. 416, 420 (Fed. Cir. 1986).

Based on the teachings of these references as a whole, as discussed above, the skilled artisan simply would not look to the complex method of Sapirstein *et al.* for wheat cultivar identification to modify the simplified procedure of Zimmerman *et al.* for human lymphocyte typing to achieve the claimed invention.

Additionally, the references teach away from their combination. For example, the Examiner’s Answer states “Sapirstein *et al.* solve a complex problem recognized by Zimmerman *et al.*, who, as noted in the rejection is concerned with simplifying the analysis of electrophoresis gels. Sapirstein *et al.* solve this problem by computer analysis and formation of a database.” This statement ignores the fundamental differences between the methods taught by Zimmerman *et al.* and Sapirstein *et al.* discussed above. This statement also ignores the fact that Zimmerman *et al.* have apparently already solved the problem of complexity using a completely different method than Sapirstein *et al.* Zimmerman *et al.* overcome the problem by actually minimizing the complexity of the results which reduces the number of bands present to “a single product in homozygous individuals or two products in heterozygous individuals.” Page 4542, top of left column. In contrast, Sapirstein *et al.*’s results produce a large number of bands whose analysis is “sufficiently tedious to require implementation by means of a computer.” Page 492, fourth paragraph. Representative results of these two techniques are shown below:



Zimmerman *et al.*

Sapirstein *et al.*

By minimizing the complexity and simplifying the interpretation of their results, Zimmerman *et al.* overcome the need for the complex solution proposed by Sapirstein *et al.* It is only because Sapirstein *et al.* have not been able to simplify their results that their analyses “require implementation by means of a computer.” Accordingly, one skilled in the art would recognize that these references teach away from each other.

The Examiner's failure to consider the references as a whole also supports the fact that there is no motivation or suggestion in the references themselves to combine their teachings, other than in impermissible hindsight. Appellants respectfully submit that the Examiner has simply used the claimed invention as a roadmap to find divergent references, only parts of which appear to suggest the claimed invention, and only thereafter sought to satisfactorily provide a motivation for their combination. Indeed, the Examiner's attempts to overcome this deficiency by stating:

[i]n this case, the practitioner would have been motivated to modify the methods of Zimmerman *et al.* in order to take advantages (sic) of the "Satisfactory precision obtainable compared to manual measurement procedures using rules or microcomparators... Rapid analysis by computerisation..." and "the facility to compare and manipulate normalised gliadin PAGE pattern (sic) using computer graphics (p.515)."

However, none of these stated problems appear to have been a concern for Zimmerman *et al.* In fact, Zimmerman *et al.* produce a banding pattern of at most "two products in heterozygous individuals." These results are easy to interpret and one skilled in the art would not need to resort to the use of microcomparators or need to perform a rapid computer analysis. Instead, the skilled artisan could easily match the position of the one or two unknown bands with the positive controls run in different lanes on the same gel as described by Zimmerman *et al.* The Examiner also attempts to overcome this lack of motivation by stating that:

[i]t would have been clear to the ordinary practitioner at the time the invention was made that such analysis would be applicable to the methods taught by Zimmerman *et al.* because Zimmerman *et al.* state that the 'identifying (sic) novel alleles is based on positive detection of HD products with unique electrophoretic mobilities (p.4545.)' Thus the ordinary practitioner would have been motivated to use a measurement method such as the ones taught by Sapirstein *et al.* in order to have provided a clear and quantitative methodology for allele identification.

However, the Examiner's statement that "[i]t would have been clear to the ordinary practitioner at the time the invention was made that such analysis would be applicable to the methods taught by Zimmerman et al..." is not a sufficient motivation to make a prima facie case of obviousness. A statement that modifications of the prior art to meet the claimed invention would have been "well within the ordinary skill of the art at the time the claimed invention was made" is not sufficient to establish a prima facie case of obviousness without some objective reason to combine the teachings of the references. *Ex parte Levengood*, 28 U.S.P.Q. 2d 1300, 1310 (Bd. Pat. App. & Inter. 1993). *See also, In re Kotzab*, 217 F. 3d 1365, 1371, 55 U.S.P.Q. 2d 1313, 1318 (Fed. Cir. 2000). No such motivation or reasoning is present in the cited references. The only motivation to combine the references as suggested by the Examiner is found in the Appellant's patent application.

Moreover, Zimmerman *et al.* achieved the Examiner's stated goal of "a clear and quantitative methodology for allele identification" without resorting to the method taught by Sapirstein *et al.* The Examiner admits as much when she states "Zimmerman *et al.* specifically teach that 'every DQA1 allele, with the exception of DQA1\*0601 can be distinguished by the unique mobility of one or both of its HD bands.'" Thus, one skilled in the art would be not be motivated to complicate the method of Zimmerman *et al.* with the methodology taught by Sapirstein *et al.* because doing so would only achieve the same end result.

The Examiner also argues that appellants are performing a "piecemeal analysis" of the references, not considering the rejection as a whole, and that "One cannot show nonobviousness by attacking references individually where the rejections are based on combination of references." Appellants respectfully disagree with this conclusion and note that a prior art reference must be considered in its entirety, including portions that would lead away from the claimed invention. *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 U.S.P.Q. 303 (Fed. Cir. 1983).

Appellants also believe that this obviousness rejection is improper for the reasons of record in appellant's Appeal Brief. Accordingly, the rejection of the claims as being obvious over Zimmerman *et al.* and Sapirstein *et al.* should be withdrawn.



**2. The claims are not obvious over Zimmerman *et al.* and Sapirstein *et al.* both in view of Mullins *et al.***

The rejection of claims 55-69 and 73-76 was also maintained “under 35 U.S.C. 103(a) as being unpatentable over Zimmerman *et al.* in view of Sapirstein *et al.* (Seed Science Technology (1986) 14(3) 489-517) both further in view of Mullins *et al.*” The teachings of Zimmerman *et al.* and Sapirstein *et al.* are discussed above. Mullins *et al.* were cited by the Examiner “merely to demonstrate that it was known in the art at the time the invention was made to determine exact numerical mobility values for heteroduplex nucleic acid molecules.”

However, the teachings of Mullins *et al.* do not overcome the deficiencies in the Examiner’s arguments and other references stated previously. Mullins *et al.* is not directed to identifying duplex DNA molecules, but is instead focused entirely on sequence diversity, that is how many differences exist between DNA molecules. Mullins *et al.* is only directed at determining how numerous differences between two DNAs are, not the identity of the actual differences. In fact, Mullins *et al.* state their “method allows the determination of sequence relatedness without resorting to sequencing analysis[.]” Page 22, lines 17-19.

Appellants also reiterate that Mullins *et al.* do not teach calculating the exact migration distance of a single DNA duplex despite the Examiner’s contention that to the contrary. The Examiner states that “in order to determine the average distance of two points, each individual distance must be determined.” However, appellants point out that calculating the exact migration distance of a heteroduplex involves more than determining the distance the heteroduplex travels. The skilled artisan would recognize that the distance measurement alone is meaningless but must be compared to some internal standard. Mullins *et al.* exemplify this by showing the values “were calculated as the average distance of migration of the two heteroduplex bands divided by the distance of migration of the homoduplex bands.” Page 50, line 37 through page 51, line 2. In this example, the migration distance of the homoduplex bands is used as the internal standard. The Examiner then tries to support her argument by stating “[f]urthermore, Mullins *et al.* exemplify the calculation of migration distances for single DNA duplexes on page 21 and figure 8, where in fact they determine exact migration

values of single heteroduplexes (lines 15-21) and the production of standard curves for later analysis using these values.” Appellants respectfully point out that the passage cited by the Examiner clearly relates to the data set forth in figures 3A and 3B, the discussion of which immediately precedes the passage cited by the Examiner. See, for example, page 20, line 4 through page 21, line 9. These same figures are discussed in Example 4, previously cited by the Examiner, which makes it clear that the migration values are based on an “average distance of two heteroduplex bands” and are not specific for either one of them alone.

One skilled in the art would clearly recognize this because amplification of nucleic acids, as performed in Mullins *et al.*, produces two strands for each amplified sequence, a plus strand and a minus strand. Because sequences are amplified from two different sources, four strands are produced, two plus strands and two minus strands where one of each is from the different sources. Hybridizing these four single nucleic acid strands gives two homoduplexes, produced by hybridizing the plus and minus strands from the same source, and two heteroduplexes, produced by hybridizing the plus strand from the first source with the minus strand from the second source and the plus strand from the second source with the minus strand from the first source. This is exactly the pattern described in Mullins *et al.* where the migration values “were calculated as the average distance of migration of the two heteroduplex bands divided by the distance of migration of the homoduplex bands.” Page 50, line 37 through page 51, line 2.

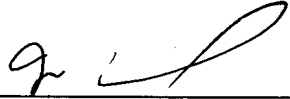
Accordingly, one skilled in the art would recognize that any migration value calculated in Mullins *et al.* is simply not capable of providing for the positive and actual identification of any of the DNA molecules in the heteroduplex bands as is required by the claimed invention. As Mullins *et al.* are cited solely for the proposition that mobility values of heteroduplexes can be measured this reference must also fail to overcome the deficiencies of Zimmerman *et al.* and Sapirstein *et al.* discussed above. Therefore, the rejection of the claims as being obvious over Zimmerman *et al.* and Sapirstein *et al.* both in view of Mullins *et al.* should be withdrawn.

# **IX. CONCLUSION**

For the foregoing reasons and reasons of record in the appellant's Appeal Brief, appellants submit that Claims 55-69 and 73-76 are patentable over the cited references, and that the final rejection of these claims should be reversed.

Respectfully submitted,

Date April 23, 2003

By 

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